IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: William J. Curatolo, et al.

SERIAL NO.: 09/918,127

FILED: July 30, 2001

FOR: Pharmaceutical Compositions Of Cholesteryl Ester Transfer Protein Inhibitors

Examiner: B. Fubara
Art Unit: 1615

Commisioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.132

I, William J. Curatolo, declare that:

1. I am a Senior Research Fellow in the Science and Technology Division at Pfizer Inc. I therefore have knowledge of the matters to which I hereinafter testify.

2. I obtained my Ph.D. in Biochemistry from Boston University in 1977, having done my thesis research in the Gastroenterology and Biophysics Group at Boston University Medical School. From 1977 to 1983, I worked at the Massachusetts Institute of Technology, first as a postdoctoral fellow in the Departments of Biology and Chemistry with Nobel Laureate H.G. Khorana, and then as a Staff Biochemist in the Biological Magnetic Resonance Group at the National Magnet Laboratory. Since 1983, I have worked for Pfizer Inc. as part of Pfizer Global Research and Development. Since 1983, I have held a variety of scientific positions at Pfizer, including manager of the Early Oral Candidates Group, the Oral Controlled Release Group, the General Pharmaceutics Group, the Biopharmaceutics (animal pharmacokinetic) Group, and the Salt Screening and Crystallization Laboratory.

3. I am an elected Fellow of the American Association of Pharmaceutical Scientists, an honor which recognizes scientific achievement in the fields of Pharmaceutics and Drug Delivery.

4. I am an inventor in and am familiar with the instant patent application. I have read the Office Action which was mailed on April 20, 2004, and am aware of the rejection of claims 1-10, 17, 18, 35-51, 56-86, and 88 over WO 99/14204 (hereinafter "Sikorski") as set forth therein.

5. Because of my experience in the field of pharmaceutical formulations technology, I would reasonably be termed as one who is skilled in the art and/or one who is an expert in that technology.

6. Sikorski contains a section starting at page 81, line 23 in which he discusses pharmaceutical compositions for oral administration. In discussing the adjuvants with which active compounds disclosed in Sikorski can be combined, Sikorski makes the following statement at page 84, lines 27-29:

> Such capsules or tablets may contain a controlled release formulation as may be provided in a **dispersion** of active compound in hydroxypropylmethyl cellulose. [Emphasis supplied]

7. Considering, *inter alia*, that (1) the above quotation refers, in context, to a controlled release formulation, (2) HPMC is well known in the art as one of the most common matrix materials for making controlled release matrix tablets, and (3) there is no disclosure in Sikorski that relates to enhancing the concentration of a poorly soluble drug, one skilled in the art would interpret Sikorski to be referring to a controlled release matrix dosage form in which hydroxypropylmethyl cellulose is the matrix material used to contain an active pharmaceutical compound from which the active compound is released in a controlled manner. Controlled release formulations generally function by slowing the release of the drug contained therein, thereby lowering the maximum concentration of dissolved drug relative to pure drug itself. In the context of controlled release, one skilled in the art could not reasonably view the quoted statement (see Paragraph 6) as referring to a solid amorphous dispersion designed to increase the concentration of the

active ingredient contained therein relative to pure drug. Rather, one skilled in the art would view Sikorski as referring to a typical controlled release formulation comprising a blend (i.e., a physical mixture) of matrix material, i.e., the HPMC Sikorski specifically mentions, plus drug that is, for example, compressed into a tablet.

8. A physical mixture of a drug and a polymer is different from a dispersion of the drug and polymer such as a solid amorphous dispersion produced by spray drying. Each individual component in a physical mixture retains the individual bulk physical properties, such as melting point, for that component. A solid amorphous dispersion of drug and a dispersion polymer has different physical properties from the individual bulk components, such as a glass transition temperature (Tg, assuming amorphous components) that is usually intermediate between the Tg for the individual components.

9. In summary, controlled release formulations do not generally increase the maximum concentration of an active pharmaceutical ingredient relative to the active ingredient alone. Nor does a controlled release formulation act to generally increase the bioavailabilty of a CETP inhibitor. Sikorski contains no disclosure relating to enhancing concentration. For these reasons, one skilled in the art could not reasonably view the statement quoted from Sikorski (see Paragraph 6) as referring to a solid amorphous dispersion. There is no disclosure in Sikorski that supports a conclusion other than the one presented herein.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Oct. 14, 2004

Date

William J. Curatolo

William J. Curatolo

CONTROLLED RELEASE OF BIOLOGICALLY ACTIVE AGENTS

RICHARD W. BAKER

Attachment 1

CONTROLLED RELEASE OF BIOLOGICALLY ACTIVE AGENTS

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A WILEY-INTERSCIENCE PUBLICATION
JOHN WILEY & SONS
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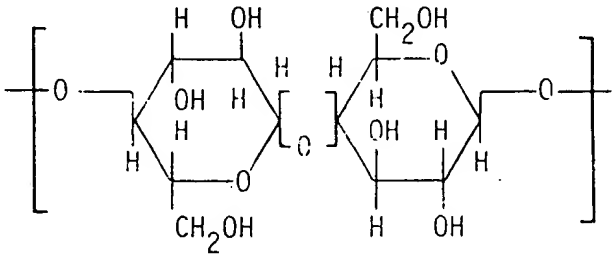
reduced by the appropriate choice of plasticizer, for which purpose di(2-ethylhexyl) phthalate is particularly widely used. Several of the more common plasticizers are listed in Table 6.5. If all the components are mutually compatible, an increase in plasticizer content at a given loading level of active agent increases the polymer chain flexibility and hence the release rate. Incompatibility between the polymer and the agent may result in a high release rate because of blooming. The addition of plasticizer may eliminate this incompatibility, reduce blooming, and consequently reduce the release rate.[69]

The PVC resin used to make these devices comes in a number of grades. If the active component is sensitive to the elevated temperatures required during oven curing, a fine high-quality plastisol-grade resin copolymerized with a small percentage of poly(vinyl acetate), to lower the fusion temperature, should be used. If the devices are to be compounded and formed using an extruder, and if cost is a consideration, as with the cat and dog flea collars described in Chapter 8, a lower grade of resin can be used.

4. CELLULOSIC POLYMERS



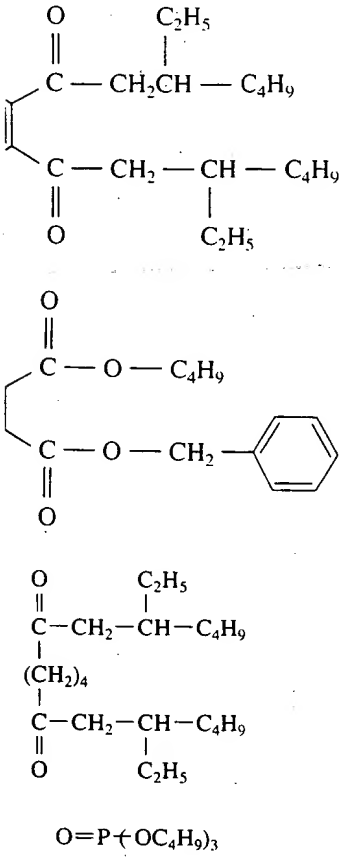
Cellulose, the structure-forming element of plant cells, is one of the most abundant of all organic polymers and has been an important chemical raw material for more than a hundred years. Its use as a membrane material dates back to Fick. In controlled release applications, cellulosic membranes are widely used in applications requiring a membrane permeable to relatively polar hydrophilic active agents.[70] Because of their high water permeability, these membranes are also used in osmotic pumping devices, described in Chapter 5.[71] Microporous cellulose triacetate films have also been investigated as monolithic dispersions for volatile oils and fragrances.[72]

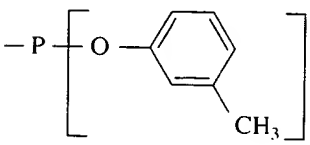
Cellulose is a polysaccharide consisting of glucose repeat units. There are three free hydroxyl groups per sugar, and all can be substituted. The properties of cellulose polymers have been extensively treated in several monographs[73,74] and a series of review articles.[75]

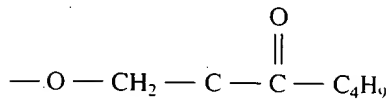
Pure cellulose, despite its free hydroxyls, does not dissolve in water, because

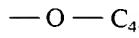
NYL CHLORIDE) PLASTICIZERS

Structure









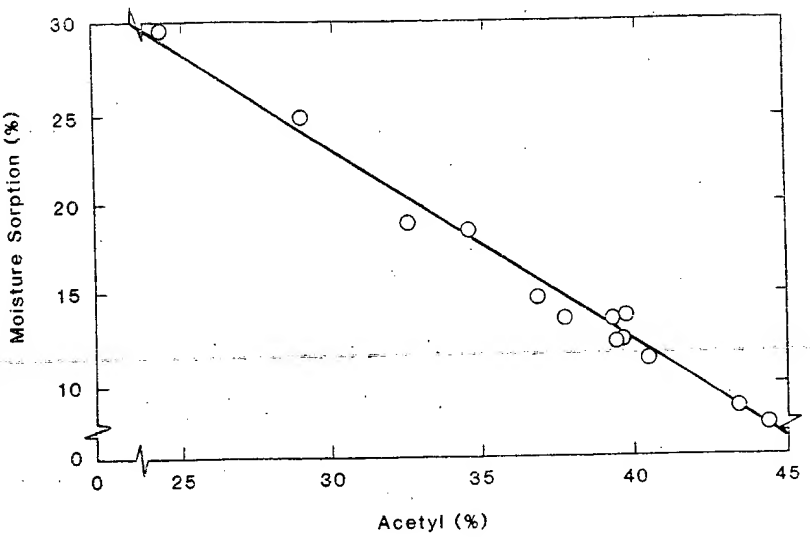


FIGURE 6.6. Moisture sorption of cellulose acetate at 95% RH, 25°C. (From Eastman Kodak.[76])

of its high crystallinity. Substitution of the hydroxyl groups with, for example, acetyl groups, decreases crystallinity by reducing the regularity of the polymer chains and increases the interchain hydrogen bonding. As the acetate content is increased, the polymer's water sorption increases until the polymer becomes water soluble at 13 wt% acetyl. Further substitution makes the polymer more hydrophobic, and the polymer again becomes water insoluble at approximately 19 wt% acetyl. The fully substituted triacetate has a relatively low water sorption of 10 wt%. A plot of the water sorption of the commercially important grades of cellulose acetate polymers versus acetyl content is given in Figure 6.6.[76] In principle, any degree of substitution of cellulose is possible, giving a very large range of

TABLE 6.6 COMMERCIALLY AVAILABLE CELLULOSE DERIVATIVES[a]

Cellulose Derivative	Degree of Substitution	Range in Substitutions (wt%)
Cellulose nitrate	2.0	10.9–11.27 nitrogen
Cellulose acetate	1.75–3.0	32–44.8 acetyl
Cellulose acetate butyrate	~2.7	12–14 acetyl, 35–39 butyryl
Cellulose acetate propionate	~2.7	2–9 acetyl, 40–49 propionyl
Ethylcellulose	2.35	40–48 ethoxyl

[a]From Bikales.[75]

RH, 25°C. (From Eastman Kodak.[76])

oxyl groups with, for example, g the regularity of the polymer ıding. As the acetate content is until the polymer becomes water kes the polymer more hydropholuble at approximately 19 wt% tively low water sorption of 10 cially important grades of celluen in Figure 6.6.[76] In principle, e, giving a very large range of

:ELLULOSE DERIVATIVES[a]

	Range in Substitutions (wt%)
	10.9–11.27 nitrogen
	32–44.8 acetyl
	12–14 acetyl, 35–39 butyryl
	2–9 acetyl, 40–49 propionyl
	40–48 ethoxyl

TABLE 6.7. EFFECT OF ACETATE CONTENT ON THE SORPTION AND DIFFUSION OF WATER, SODIUM CHLORIDE (NaCl), AND SODIUM SULFATE (Na_2SO_4) IN CELLULOSE ACETATE MEMBRANES[a]

	Acetyl Content (%)						
	33.6	37.6	38.3	39.5	39.8	41.0	43.2
				Water			
D (cm²/sec)	5.7×10^{-6}	2.9×10^{-6}		1.5×10^{-6}	1.6×10^{-6}		1.3×10^{-6}
C	0.29	0.20	~0.19	0.17	0.16	0.15	0.12
DK (cm²/sec)	16×10^{-7}	5.7×10^{-7}		2.6×10^{-7}	2.6×10^{-7}		1.5×10^{-7}
				NaCl			
D (cm²/sec)	2.9×10^{-8}	4.3×10^{-9}			9.4×10^{-10}		3.9×10^{-11}
K	0.17	0.062			0.035		0.015
DK (cm²/sec)	4.9×10^{-9}	2.7×10^{-10}			3.3×10^{-11}		5.8×10^{-1}
				Na_2SO_4			
D (cm²/sec)	1.01×10^{-8}		1.03×10^{-9}		7.2×10^{-10}	3.4×10^{-10}	
K	0.039		0.027		0.0013	0.00031	
DK (cm²/sec)	4.0×10^{-10}		2.8×10^{-12}		9.3×10^{-13}	1.07×10^{-13}	

[a]From Lonsdale et al.[77,80]

properties. However, commercially available polymers are limited to the relatively small range of compositions shown in Table 6.6.

Workers involved with reverse osmosis have been quite interested in cellulosic polymers because of their high water permeability and low salt permeability. In particular, they have studied cellulose acetate[77-79] and have determined diffusion and permeability data for water and a number of other solutes. However, the values reported vary substantially, principally because of differences in the techniques used to prepare the membrane. Some of the more reliable data are summarized in Table 6.7.[77,80] As shown, the membrane permeability properties depend to a striking degree on acetate content. Diffusion and distribution coefficient data have also been measured for a number of organic solutes by Lonsdale et al.[81] and Anderson et al.[82] These data are tabulated in Table 6.8.

TABLE 6.8. DIFFUSION AND SORPTION OF ORGANIC SOLVENTS IN CELLULOSE ACETATE AND CELLULOSE ACETATE BUTYRATE MEMBRANES[a]

Solute	Membrane	$D \times 10^{10}$ (cm^2/sec)	K
Phenol	CA[b]	10	37 ± 1
	CAB[c]	1.5	51 ± 1
2,4-Dichlorophenol	CA	1.5	332 ± 7
	CAB	0.7	405 ± 5
p-Bromophenol	CA	3.8	165 ± 2
	CAB	0.84	175 ± 2
Acetone	CA	300	0.3 ± 0.1
	CAB	100	0.49 ± 0.05
Hydroquinone	CA		3.5 ± 0.2
	CAB		5.4 ± 1.5
Nitromethane	CA	150	2.1 ± 0.5
	CAB	100	4.0 ± 0.6
Nitrobenzene	CA	8.0	54 ± 4
	CAB	3.5	105 ± 5
Pyridine	CA	75	0.7
	CAB	50	1.33 ± 0.03
Urea	CA	130	0.49 ± 0.03
Aniline	CA	20	20 ± 2
	CAB	3.5	52 ± 3
3,5-Di(carbethoxy)phenol	CA	1.8	129 ± 12
	CAB		110 ± 10

[a] Reprinted with permission from Anderson et al., *J. Phys. Chem.* **76**, 4006. Copyright 1972 American Chemical Society.
[b] CA, cellulose acetate
[c] CAB, cellulose acetate butyrate

RELEASE DEVICES

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0.7	405 ± 5
3.8	165 ± 2
0.84	175 ± 2
300	0.3 ± 0.1
100	0.49 ± 0.05
	3.5 ± 0.2
	5.4 ± 1.5
150	2.1 ± 0.5
100	4.0 ± 0.6
8.0	54 ± 4
3.5	105 ± 5
75	0.7
50	1.33 ± 0.03
130	0.49 ± 0.03
20	20 ± 2
3.5	52 ± 3
1.8	129 ± 12
	110 ± 10

s. *Chem.* **76,** 4006. Copyright 1972 American

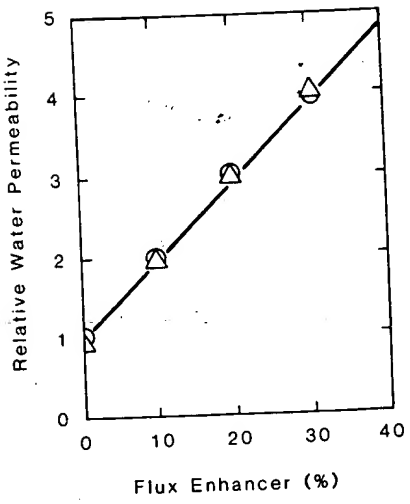
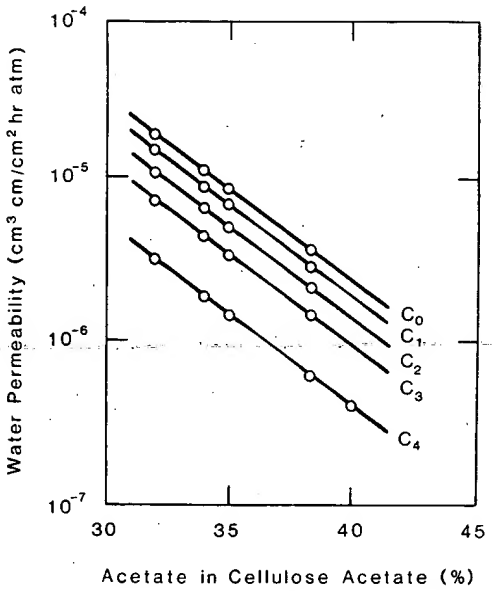


FIGURE 6.7. Effect of the flux enhancer poly(ethylene glycol) 400 (PEG 400) on the water permeability of cellulose acetate membranes relative to the permeability of the pure polymer. (From Theeuwes and Ayer.[83])

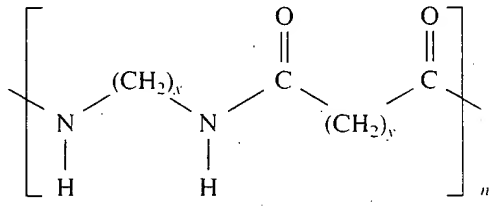
The preparation of osmotic pumping devices often requires membranes with very high water permeabilities. Cellulose acetate membranes are used in this application because the water permeability is high and can be easily adjusted by varying the degree of acetylation of the polymer. The permeability of these membranes can be increased further by adding plasticizers to the polymer to increase the water diffusion coefficient or by adding hydrophilic flux enhancers, which increase the water sorption of the membrane. Some hydrophilic plasticizers serve both purposes. The effect of the hydrophilic plasticizer poly(ethylene glycol) (PEG 400) on the osmotic water permeability of cellulose acetate membranes is shown in Figure 6.7. The water permeability is increased more than fourfold by the addition of the PEG 400. Addition of the hydrophilic polymer hydroxybutyl methyl cellulose to the cellulose acetate membranes has a similar effect, as shown in the results in Figure 6.8.[83]



Membrane:	Cellulose Acetate (%)	PEG 400 (%)	Poly Oxypropylene Glycol 950 (%)	Hydroxy Butyl Methyl Cellulose (%)
C_0	59.6	12.8	2.1	25.5
C_1	68.1	12.8	2.1	17.0
C_2	76.6	12.8	2.1	8.5
C_3	85.1	12.8	2.1	–
C_4	100.0	–	–	–

FIGURE 6.8. Effect of plasticizer and additives on the osmotic water permeability of cellulose acetate membranes. (From Theeuwes and Ayer.[83])

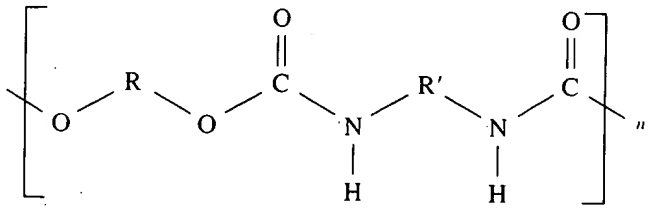
5. POLYAMIDES



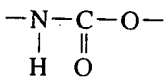
Polyamides, or nylons, are prepared by condensation of a diacid and a diamine or the self-condensation of an amino acid derivative. Most nylons are crystalline, with significant interchain hydrogen bonding. This makes them difficult to dissolve. Their polar nature makes nylons relatively hydrophilic, and water sorptions usually range from 5 to 10 wt%.

An atypical nylon was prepared by Allan et al.[84] by condensing dilinoleic acid and ethylene diamine. The large unsaturated acid monomer causes the polymer to be noncrystalline and relatively low melting, and to provide useful permeability. Monolithic devices containing an insecticide solution were prepared that provided release of the active component for almost a year. Structurally irregular nylons have also been prepared by interfacial polymerization techniques, described in Chapter 7. The permeability of microcapsules thus prepared is also relatively high.[85]

6. POLYURETHANES



Urethanes characteristically contain the grouping



and are prepared by reacting diisocyanates with diols via the reaction

$$HO{-}R{-}OH + OCN{-}R'{-}NCO \longrightarrow \text{+}O{-}R{-}OCONH{-}R'{-}NHCO\text{+}_n$$

If R and R′ are small, nylon-like polymers are obtained, but more frequently the diol used is a low-molecular-weight hydroxy-terminated oligomer of a polyether or polyester. The polymerization reaction then produces polyether or polyester blocks linked by isocyanate sections. These segmented polyester-based or polyether-based polyurethanes are rubbery, relatively permeable elastomers. They are used in controlled release devices because the hydrophilic-to-hydrophobic ratio in the polymer can be balanced to obtain the optimum permeability properties.[86,87] Incorporating trifunctional groups into the reaction mixture produces a cross-linked polymer. Wilkes has recently published a review of urethane chemistry.[88]

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CHAPTER 37

Powders

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Powders are encountered in almost every aspect of pharmacy, both in industry and in practice. Drugs and other ingredients, when they occur in the solid state in the course of being processed into a dosage form, usually are in a more or less finely divided condition. Frequently, this is a powder whose state of subdivision is critical in determining its behavior both during processing and in the finished dosage form. Apart from their use in the manufacture of tablets, capsules, and suspensions, powders also occur as a pharmaceutical dosage form. Although the use of powders as a dosage form has declined, the properties and behavior of finely divided solid materials are of considerable importance in pharmacy.

This chapter is intended to provide an introduction to the fundamentals of powder mechanics and the primary means of powder production and handling. The relationships of the principles of powder behavior to powders as dosage forms are discussed.

PRODUCTION METHODS

Molecular Aggregation

PRECIPITATION AND CRYSTALLIZATION

The precipitation and crystallization processes are fundamentally similar and depend on achieving three conditions in succession: a state of supersaturation (super cooling in the case of crystallization from a melt), formation of nuclei, and growth of crystals or amorphous particles.

Supersaturation can be achieved by evaporation of solvent from a solution, cooling of the solution if the solute has a positive heat of solution, production of additional solute as a result of a chemical reaction, or a change in the solvent medium by addition of various soluble secondary substances. In the absence of seed crystals, significant supersaturation is required to initiate the crystallization process through formation of nuclei. A nucleus is thought to consist of from 10 to a few hundred molecules having the spatial arrangement of the crystals that will be grown ultimately from them.

Such small particles are shown by the Kelvin equation to be more soluble than large crystals; therefore, they require supersaturation, relative to large crystals, for their formation and subsequent growth. It is a gross oversimplification to assume that, for a concentration gradient of a given value, the rate of crystallization is the negative of the rate of dissolution. The latter is generally somewhat greater.

Depending on the conditions of crystallization, it is possible to control or modify the nature of the crystals obtained. When polymorphs exist, careful temperature control and seeding with the desired crystal form are often necessary. The habit or shape of a given crystal form often highly depends on impurities in solution, pH, rate of stirring, rate of cooling, and the solvent. Very rapid rates of crystallization can result in impurities being included in the crystals by entrapment.

SPRAY-DRYING

Atomization of a solution of one or more solids via a nozzle, spinning disk, or other device, followed by evaporation of the solvent from the droplets is termed *spray-drying*. The nature of the powder that results is a function of several variables, including the initial solute concentration, size distribution of droplets produced, and rate of solvent removal. The weight of a given particle is determined by the volume of the droplet from which it was derived and by the solute concentration. The particles produced are aggregates of primary particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal. This approach to the powdered state provides the opportunity to incorporate multiple solid substances into individual particles at a fixed composition, independent of particle size, and avoiding difficulties that can arise in attempting to obtain a uniform mixture of several powdered ingredients by other procedures.

Particle-Size Reduction

Comminution in its broadest sense is the mechanical process of reducing the size of particles or aggregates. Thus, it embraces a wide variety of operations including cutting, chopping, crushing, grinding, milling, micronizing, and trituration, which depend primarily on the type of equipment employed. The selection of equipment in turn is determined by the characteristics of the material, the initial particle size and the degree of size reduction desired. For example, very large particles may require size reduction in stages simply because the equipment required to produce the final product will not accept the initial feed, as in crushing prior to grinding. In the case of vegetable and other fibrous material, size reduction generally must be, at least initially, accomplished by cutting or chopping.

Chemical substances used in pharmaceuticals, in contrast, generally need not be subjected to either crushing or cutting operations prior to reduction to the required particle size. How-

ever, these materials do differ considerably in melting point, brittleness, hardness, and moisture content, all of which affect the ease of particle-size reduction and dictate the choice of equipment. The heat generated in mechanical grinding, in particular, presents problems with materials that tend to liquefy or stick together and with the thermolabile products that may degrade unless the heat is dissipated by use of a flowing stream of water or air. The desired particle size, shape, and size distribution also must be considered in the selection of grinding or milling equipment. For example, attrition mills tend to produce spheroidal, more free-flowing particles than do impact-type mills, which yield more irregular-shaped particles.

FRACTURE MECHANICS

Reduction of particle size through fracture requires application of mechanical stress to the material to be crushed or ground. Materials respond to stress by yielding, with consequent generation of strain. Depending on the time course of strain as a function of applied stresses, materials can be classified according to their behavior over a continuous spectrum ranging from brittle to plastic. In the case of a totally brittle substance, complete rebound would occur on release of applied stress at stresses up to the yield point, where fracture would occur. In contrast, a totally plastic material would not rebound nor would it fracture.

The vast majority of pharmaceutical solids lie somewhere between these extremes and thus possess both elastic and viscous properties. Linear and, to a lesser extent, nonlinear viscoelastic theory has been developed well to account for quantitatively and explain the simultaneous elastic and viscous deformations produced in solids by applied stresses.

The energy expended by comminution ultimately appears as surface energy associated with newly created particle surfaces, internal free energy associated with lattice changes, and as heat. Most of the energy expressed as heat is consumed in the viscoelastic deformation of particles, friction, and in imparting kinetic energy to particles. Energy is exchanged among these modes and some is, of course, effective in producing fracture. It has been estimated that 1% or less of the total mechanical energy used is associated with newly created surface or with crystal lattice imperfections.

Although the grinding process has been described mathematically, the theory of grinding has not been developed to the point where the actual performance of the grinding equipment can be predicted quantitatively. However, three fundamental laws have been advanced:

Kick's Law—The work required to reduce the size of a given quantity of material is constant for the same reduction ratio regardless of the original size of the initial material.

Rittinger's Law—The work used for particulate size reduction is directly proportional to the new surface produced.

Bond's Law—The work used to reduce the particle size is proportional to the square root of the diameter of the particles produced.

In general, however, these laws have been useful only in providing trends and qualitative information on the grinding process. Usually laboratory testing is required to evaluate the performance of particular equipment. A work index, developed from Bond's Law, is a useful way of comparing the efficiency of milling operations.[1] A grindability index, which has been developed for a number of materials, also can be used to evaluate mill performance.[2]

A number of other factors also must be considered in equipment selection. Abrasion or mill wear is an important factor in the grinding of hard materials, particularly in high-speed, close-clearance equipment (eg, hammer mills). In some instances mill wear may be so extensive as to lead to highly contaminated products and excessive maintenance costs that make the milling process uneconomical. Hardness of the material, which often is related to abrasiveness, also must be considered. This usually is measured on the Moh's scale.

Qualitatively, materials from 1 to 3 are considered as soft and from 8 to 10 as hard. Friability (ease of fracture) and fibrousness can be of equal importance in mill selection. Fibrous materials, such as plant products, require a cutting or chopping action and usually cannot be reduced in size effectively by pressure or impact techniques. A moisture content above about 5% will in most instances also create a problem and can lead to agglomeration or even liquefaction of the milled material. Hydrates often will release their water of hydration under the influence of a high-temperature milling process and thus may require cooling or low-speed processing.

METHODS AND EQUIPMENT

When a narrow particle-size distribution with a minimum of fines is desired, closed-circuit milling is advantageous. This technique combines the milling equipment with some type of classifier (see *Particle-Size Measurement and Classification*). In the simplest arrangement, a screen is used to make the separation, and the oversize particles are returned to the mill on a continuous basis while the particles of the desired size pass through the screen and out of the grinding chamber. Over-milling, with its subsequent production of fines, thereby is minimized. Equipment also has been designed to combine the sieving and milling steps into a single operation (see *Centrifugal-Impact Mills and Sieves*).

To avoid contamination or deterioration, the equipment used for pharmaceuticals should be fabricated of materials that are chemically and mechanically compatible with the substance being processed. The equipment should be easy to disassemble for cleaning to prevent cross-contamination. Dust-free operation, durability, simplified construction, and operation and suitable feed and outlet capacities are additional considerations in equipment selection.

Although there is no rigid classification of large-scale comminution equipment, it generally is divided into three broad categories based on feed and product size:

1. *Coarse crushers* (eg, jaw, gyratory, roll, and impact crushers).
2. *Intermediate grinders* (eg, rotary cutters, disk, hammer, roller, and chaser mills).
3. *Fine grinding mills* (eg, ball, rod, hammer, colloid, and fluid-energy mills; high-speed mechanical screen and centrifugal classifier).

Machines in the first category are employed ordinarily where the size of the feed material is relatively large, ranging from 1½ to 60 inches in diameter. These are used most frequently in the mineral crushing industry and will not be considered further. The machines in the second category are used for feed materials of relatively small size and provide products that fall between 20- and 200-mesh. Those in the third category produce particles, most of which will pass through a 200-mesh sieve, although often the particle size of the products from fine grinding mills is well into the micron range.

The comminution effect of any given operation can be described mathematically in terms of a matrix whose elements represent the probabilities of transformation of the various-size particles in the feed material to the particle sizes present in the output. The numerical values of the elements in the transition matrix can be determined experimentally and the matrix serves to characterize the mill. Matrices of this type are frequently a function of feed rate and feed particle-size distribution but are useful in predicting mill behavior. Multiplication of the appropriate comminution matrix with the feed-size distribution line-matrix yields the predicted output-size distribution.

INTERMEDIATE AND FINE GRINDING MILLS

The various types of comminuting equipment in this class generally employ one of three basic actions or, more commonly, a combination of these actions.